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Mathematical Modeling and Dynamics of HIV Progression and Treatment*

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Abstract: This article presents a brief review on the modeling and dynamics of HIV infection in vivo. We introduce typical mathematical models on the interaction between $CD4^+$ T-cells and virus particles, as well as the drug therapy. We focus on theoretical results and simulations of ODEs, DDEs, integro-differential equations and impulsive differential equations. Parameter values of those models are collected in a table for reader's reference.

Keywords: HIV; T-cells; drug resistance; drug therapy; time delay; asymptotic stability

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1 Introduction

AIDS (Acquired Immunodeficiency Syndrome) is one of the most serious, deadly diseases in human history. AIDS, caused by the human immunodeficiency virus (HIV), has spread in successive waves in various regions around the globe. The estimated number of persons living with HIV worldwide in 2008 was 33.4 million. The number of newly infected with HIV in 2008 is 2.7 million[1].

HIV needs bonding to the specific host cell receptor. The receptor is a CD4 antigen in the membrane of T helpers lymphocytes. When the cell is activated by an antigenic impulse, viral protease finishes the process of releasing the virus. These new virions immediately attack next $CD4^+$ T-cells and leads to their destruction. The immune system is exhausted by acceleration of the $CD4^+$ production and destruction, and soon the destruction predominates. The deep $CD4^+$ count decreasing (under $200/mm^3$) is strongly associated with the risk of development of opportunistic infections.

Although treatments for AIDS and HIV can slow AIDS progression, there is currently no vaccine or cure. The fact that HIV replicates rapidly, producing on average 10^{10} viral particles per day, leads to the realization that HIV evolves so rapidly that treatment with a single drug is bound to fail[2]. Highly Active Antiretroviral Therapy (HAART) is the recommended treatment for HIV infection. HAART combines three or more anti-HIV medications in a daily regimen. The drugs are unable to eradicate virus from the body, but they can minimize viral replication, restore immunological function, improve quality of life and reduce morbidity and mortality. These drug cocktails generally consist of reverse transcriptase (RTIs) and protease

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inhibitors (PIs). RTIs can block the infection of target T-cells by infectious virus, and PIs can prevent HIV protease from cleaving HIV polyprotein into functional units, causing infected cells to produce virus particles that are noninfectious. There are another two new agents recently: entry inhibitors and integrase inhibitors.

Viral mathematical models can provide insights into the dynamics of viral load in vivo, and may play a significant role in the development of a better understanding of diseases and various drug therapy strategies against them. Perelson and Nelson[2], Nowak and May[3] provide excellent reviews and many more citations on HIV treatment. This review paper will give a brief introduction to modeling and dynamics on the interaction between HIV and $CD4^+$ T-cells. The main attention is paid to mathematical analysis of interaction between T-cells, antiviral immune system responses, drug therapy and viral load. Furthermore, theoretical results and methods of viral microcosmic models are included in paper[4]. For convenience, we use T-cells instead of $CD4^+$ T-cells in the rest parts of the paper.

2 Basic models with logistic T-cells growth and immune response

2.1 The basic model and the extension

We begin with a very simple model, which captures essential features of HIV. The basic model of viral dynamics has three variables: uninfected T-cells concentration at time t, $T(t)$; infected T-cells concentration at time t, $T^*(t)$; free viral particles concentration at time t, $V(t)$. Uninfected T-cells are produced at a constant rate, λ, and die at a rate dT. Free virus infects uninfected T-cells to produce infected T-cells at rate kTV. Infected cells die at rate δT^*. New virus is produced from infected cells at rate $N\delta T^*$ and dies at rate cV. The average life-times of uninfected T-cells, infected T-cells, and free virus are given by $1/d$, $1/\delta$, and $1/c$, respectively. The average number of virus particles produced over the lifetime of a single infected T-cell (the burst size) is given by N. These assumptions lead to the following differential equations

$$\begin{aligned} T'(t) &= \lambda - dT - kVT, \\ T^{*'}(t) &= kVT - \delta T^*, \\ V'(t) &= N\delta T^* - cV. \end{aligned} \tag{1}$$

Model (1) has been studied in [3,5-7]. (1) has an uninfected steady state $E_0(\lambda/d, 0, 0)$. The crucial quantity is the basic reproductive ratio, $\mathcal{R}_0 = (kN\lambda)/(cd)$. R_0 is the average number of newly infected cells that arise from one infected cell when almost all cells are uninfected. When $\mathcal{R}_0 < 1$, the uninfected steady state E_0 is locally asymptotically stable; when $\mathcal{R}_0 > 1$, E_0 is unstable while the infected steady state $\bar{E} = (\lambda/(d\mathcal{R}_0), cd(\mathcal{R}_0 - 1)/(kN\delta), d(\mathcal{R}_0 - 1)/k)$ exists and is locally asymptotically stable.

Considering the density-dependent proliferation rate of T-cells[8], logistic growth has been included in other models to describe the growth of healthy T-cells[2,9-12]. In 2003, De Leenheer and Smith[9] summarized a competitive model reflecting the interaction between T-cells and

virus particles, given by following equations

$$\begin{aligned} T'(t) &= f(T) - kVT, \\ T^{*'}(t) &= kVT - \delta T^*, \\ V'(t) &= N\delta T^* - cV - ikVT, \end{aligned} \tag{2}$$

where

$$f(T) = \lambda - dT + rT\Big(1 - \frac{T}{T_{\max}}\Big), \quad \text{or} \quad f(T) = \lambda - dT, \quad \text{and} \quad i = 0, \quad \text{or} \quad i = 1.$$

r is the growth rate ($r > d$ in general), and $T_{\max}$ is the carrying capacity. Using the theory of competitive (and cooperate) systems by Hirsch and Smith (see [9] and the references therein), those authors obtained the basic reproduction number $\mathcal{R}_0 = KT_0(N - i)/c$ (T_0 is the normal target cell level at the uninfected steady state) for model (2) and got following results.

1) If $\mathcal{R}_0 < 1$, the disease-free steady state is globally stable and the virus is cleared, which does not depend on the form of $f(T)$.

2) If $\mathcal{R}_0 > 1$ and $f(T) = \lambda - dT$, then a chronic disease steady state exists which is globally asymptotically stable under certain conditions.

3) If $\mathcal{R}_0 > 1$ and

$$f(T) = \lambda - dT + rT\Big(1 - \frac{T}{T_{\max}}\Big),$$

there exists an orbitally asymptotically stable periodic orbit, which attracts almost all solutions under suitable conditions.

It was shown tnhat particular choices for $f(T)$ may lead to different qualitative behavior. For example, for $f(T) = \lambda - dT$, the chronic disease steady state, if it exists, is always locally asymptotically stable, while for

$$f(T) = \lambda - dT + rT\Big(1 - \frac{T}{T_{\max}}\Big),$$

this steady state may be unstable and sustained oscillations may occur[9]. This sensitivity of the behavior to $f(T)$, in particular, calls for a better understanding of the mechanisms of T-cells proliferation.

Wang and Ellermeyer studied a model with a full logistic proliferation term $rT(1 - \frac{T+T^*}{T_{\max}})$ and got the stability of infected steady state depending on the size of the T-cells proliferation rate[10]. Culshaw and Ruan chose N as a bifurcation parameter and obtained a restriction N_{crit} on the number of viral particles released per infectious cell in order for infection to be sustained[11]. Wang and Li[12] obtained the global stability of the positive equilibrium by the compound matrices method.

2.2 Immune response

For most virus infections, cytotoxic T lymphocytes (CTLs) play a critical role in antiviral defense by attacking virus-infected cells. It is believed that they are the main host immune factor tnhat limits the extent of virus replication in vivo and thus determines virus load[6]. The

mathematical model with CTLs is a system of differential equations

$$\begin{aligned} T'(t) &= \lambda - dT - kVT, \\ T^{*'}(t) &= kVT - \delta T^* - qT^*C, \\ V'(t) &= N\delta T^* - cV, \\ C'(t) &= g(T, T^*, C) - d_C C, \end{aligned} \tag{3}$$

where $C(t)$ denotes the concentration of CTLs at time t, and d_C is the death rate of CTLs. Infected T-cells die at a per capita rate δ and are killed by CTLs with a rate qT^*C. The function $g(T, T^*, C)$ describes the rate of activation of the immune response (CTLs). It has been suggested that $g(T, T^*, C)$ can have one of the following three forms[6,9,13]

$$g(T, T^*, C) = pT^*, \quad g(T, T^*, C) = pT^*C, \quad g(T, T^*, C) = pTT^*C,$$

where p is the rate of stimulation of CTLs. It is still unknown which $g(T, T^*, C)$ is better to describe the activation of CTLs. Based on this simple model and simulations, Nowak and Bangham explained that CTL responsiveness determines virus load, but there may be no obvious correlation between virus load and the abundance of antiviral CTLs[6]. They showed that a better indicator of CTL responsiveness is the equilibrium virus load, rather than the abundance of virus-specific CTLs.

3 Time delay

It is well known that delay differential equations (DDEs) exhibit much more complicated dynamics than ODEs since a delay may cause the stability change and oscillation. Actually, time delay occurs in the progression of HIV infection. In studying the viral clearance rates, Perelson *et al*[5] assumed that there are two types of delays, pharmacological delay and intracellular delay, which occur between the administration of drug and the observed decline in viral load. The pharmacological delay is the time from drug administration to the entry of the virus within the target cell. The intracellular delay is the time required for an infected cell to replicate (the time interval that the virus binds to the receptors of the target cell to the time the first virion is produced from the same target cell).

3.1 Discrete delay

In 1996, Herz *et al*[14] used a discrete delay to model the intracellular delay in the basic HIV model and showed that the incorporation of a delay would substantially shorten the estimated half-life of the free virus. Nelson *et al*[15] found that the predicted rate of decline in plasma virus concentration depends on three factors: the death rate of virus producing cells, the efficacy of therapy, and the length of the delay if an intracellular delay and drug therapy are included.

Culshaw and Ruan extended the basic model to incorporate the logistic growth and an intracellular delay[11]. They demonstrated that the stability of the infected steady state is not affected by the modification with realistic parameter values. However, they did find conditions that lead to a Hopf bifurcation if parameter intervals are beyond certain intervals. We will show a delay model and its dynamics in Section 4.

3.2 Continuous delay

We often use gamma distribution to represent multistage processes. We can assume that the probability distribution of infected T-cells death is given by a gamma distribution, which suggests that the death of infected T-cells only occurs after a number of subprocesses are completed[2]. A gamma distribution function is used to describe a continuous delay between infection and viral production[16, 17]. Nelson and Perelson[16] constructed an integro-differential equation and showed that the value for δ estimated from patient data was directly influenced by the assumed variance and mean of the gamma distribution, and concluded by presenting a general result on the stability of a set of DDEs. Mittler *et al*[17] showed that good estimates for free viral clearance rates, infected cell death rates, and parameters characterizing the gamma distribution can be obtained. They demonstrated that it is possible to incorporate distributed intracellular delays into existing models for HIV dynamics and to use these refined models to estimate the half-life of free virus from data.

4 Drug therapy

4.1 Combination therapy

Research has shown that using combinations of drugs is a better treatment strategy than using only one or two drugs[2]. We focus on HIV models with the combination of RTIs and PIs in order to reduce the amount of virus in their bodies. Let n_{rt} and n_p be the drug efficacy of RTIs and PIs, respectively. We assume the drug efficacy is less than 100% in the following models.

Based on system (2), De Leenheer and Smith[9] studied the following model with constant drug therapy

$$\begin{aligned} T'(t) &= f(T) - k(1-n_{rt})V_I T, \\ T^{*'}(t) &= k(1-n_{rt})V_I T - \delta T^*, \\ V_I'(t) &= (1-n_p)N\delta T^* - ikV_I T - cV_I, \\ V_{NI}'(t) &= n_p N\delta T^* - cV_{NI}. \end{aligned} \tag{4}$$

The basic reproduction number of (4) is $\mathcal{R}_0^c = kT_0[N(1-n_{rt})(1-n_p)-i]/c$. Similar conclusions as those for system (2) were obtained. We continue to investigate the interaction between T-cells and virus load with drug therapy. We formulate the model with HIV pathogenesis within-host, adding the combined effects of drug therapy (RTIs and PIs), an intracellular delay and logistic growth[4]

$$\begin{aligned} T'(t) &= \lambda - dT(t) + rT(t)\Big(1 - \tfrac{T(t)}{T_{\max}}\Big) - k_I(1-n_{rt})V_I(t)T(t), \\ T^{*'}(t) &= k_A(1-n_{rt})V_I(t-\tau)T(t-\tau) - \delta T^*(t), \\ V_I'(t) &= (1-n_p)N\delta T^*(t) - cV_I(t), \\ V_{NI}'(t) &= n_p N\delta T^*(t) - cV_{NI}(t). \end{aligned} \tag{5}$$

The parameter k_I represents the rate of infection of T-cells with free virus, and k_A is the rate at which infected cells become actively infected. We assume that $dT_{\max} > \lambda$, the number of

T-cells will decrease if it surpasses $T_{\max}$. The dynamics of system (5) is fully determined by the first three equations since

$$V_{NI}(t) = \mathrm{e}^{-ct}\Big(V_{NI}(0) + \int_0^t \mathrm{e}^{c\tau} n_p N\delta T^*(\tau)\mathrm{d}\tau\Big).$$

The initial conditions are

$$T(\theta) = \varphi_1(\theta) \geq 0, \quad T^*(0) = \varphi_2 \geq 0, \quad V_I(\theta) = \psi(\theta) \geq 0 \quad \text{for} \quad \theta \in [-\tau, 0], \tag{6}$$

where φ_2 is a given constant, and $\varphi_1, \psi \in C([-\tau, 0], R_+)$ with $R_+ = [0, +\infty]$. It can be verified that if $(T(t), T^*(t), V_I(t))$ is a solution with initial conditions (6), then $T(t) \geq 0$, $T^*(t) \geq 0$, $V_I(t) \geq 0$ for all $t \geq 0$. Let

$$\eta_c = 1 - (1 - n_{rt})(1 - n_p), \quad \eta_{crit} := 1 - \frac{c}{k_A N T_0}.$$

Then $\eta_c < \eta_{crit}$ ensures the existence of the infected (positive) steady state $\bar{E}$.

We obtained the transcendental characteristic equation $F_1(\xi)$ of the linearized system at the infected steady state $\bar{E}$. When $\tau = 0$, we got the asymptotic stability condition of $\bar{E}$ by Routh-Hurwitz criterion. When $\tau > 0$, using Kuang's theory of DDEs[18], we proved that $F_1(\xi)$ can not have a purely imaginary root under certain conditions, and the infected steady state $\bar{E}$ is locally asymptotical stable. Under other conditions we concluded that the characteristic equation $F_1(\xi)$ has a pair of purely imaginary roots $\pm i\omega_0$. We proved the occurrence of a Hopf bifurcation at the positive equilibrium $\bar{E}$. Let $\xi(\tau) = x(\tau) + iy(\tau)$ be the root of $F_1(\xi)$, and

$$S = \mathrm{sign}\Big\{\frac{\mathrm{d}}{\mathrm{d}\tau}(\mathrm{Re}\,\xi(\tau))\Big\}_{\xi=i\omega_0} = \mathrm{sign}\Big\{\mathrm{Re}\Big(\frac{\mathrm{d}\xi(\tau)}{\mathrm{d}\tau}\Big)^{-1}\Big\}_{\xi=i\omega_0}.$$

Differentiate $F_1(\xi)$ with respect to τ and combine the above formula, we can obtain sufficient conditions to satisfy $S > 0$ (the transversality condition).

By the theory of DDEs, sufficient conditions are established for the local asymptotic stability of the uninfected steady state and the infected steady state. Furthermore, by constructing Lyapunov function, we obtained the global asymptotic stability of uninfected steady state when $\eta_c > \eta_{crit}$. The influence of the time delay on the stability of equilibrium states is discussed. We showed that the local stability of the uninfected steady state is independent of the size of the delay; on the other hand, we proved that increasing the delay can destabilize the infected steady state leading to a Hopf bifurcation of periodic solutions. This clearly shows the importance of time delay on HIV dynamics under treatment.

In simulation, we have parameters $\lambda = 10$ cells $\mathrm{mm}^{-3}\mathrm{day}^{-1}$, $\delta = 0.26$ day^{-1} and $T_{\max} = 1500$ mm^{-3} fixed[4], and choose three sets of data: $n_{rt} = 0.4$, $n_p = 0.3$; $n_{rt} = 0.5$, $n_p = 0.55$ and $n_{rt} = 0.6$, $n_p = 0.8$; then $\eta_c = 0.5800$, $\eta_c = 0.7750$ and $\eta_c = 0.9200$, respectively. The numerical simulations show that increasing the combination drug efficacy can increase the total number of healthy and infected T-cells and decrease the number of the infectious virus (see Figure 1). In other case, we choose $n_{rt} = 0.6$, $n_p = 0.7$, then $\eta_c = 0.8800$ and $\eta_c < \eta_{crit}$. Comparing to Culshaw and Ruan[11], we found a Hopf bifurcation in realistic parameter values (see Figure 2). Similar conclusion can be obtained if we use the full logistic growth of healthy T-cells in model (5). Our model is an extension of Culshaw and Ruan[11].

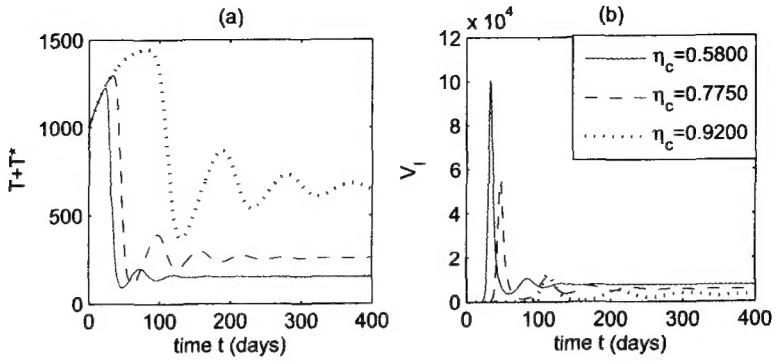

Figure 1: *Local asymptotic stability of the infected steady state $\bar{E}$. $d = 0.007\ day^{-1}$, $r = 0.03\ day^{-1}$, $k_I = 2.4 \times 10^{-5}\ mm^3 day^{-1}$, $k_A = 2.0 \times 10^{-5}\ mm^3 day^{-1}$, $N = 2500$, $c = 2.4\ day^{-1}$, $\tau = 1.5$ days, and η_c changes from 0.5800 to 0.9200. As η_c increases, the total number of the healthy and infected T-cells (a) increases dramatically, while the number of the infectious virions (b) decreases substantially*

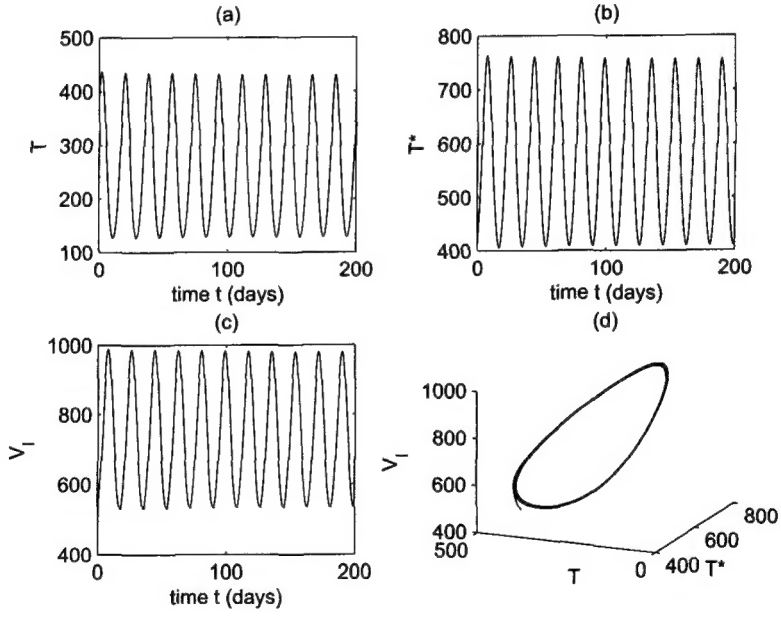

Figure 2: *Periodic solutions bifurcated from the infected steady state $\bar{E}$. $d = 0.03\ day^{-1}$, $r = 0.95\ day^{-1}$, $k_I = 0.0027$ virions $mm^3 day^{-1}$, $k_A = 0.0020$ virions $mm^3 day^{-1}$, $N = 50$, $c = 3\ day^{-1}$ and $\tau = 1.5 > \tau_0 \approx 1.3395$*

The constant efficacy of RTIs and PIs is only a simple assumption in modeling HIV treatment. The efficacy of antiviral treatment varies with time and other factors. Mathematical models have been developed to study the pharmacokinetics of drug therapies[19,20]. Huang *et*

al[20] formulated a model to illustrate the relationship between antiviral response and pharmacokinetics, time-varying adherence and drug resistance by simulation experiments. They discussed the properties of the viral dynamics and studied how time-varying treatment efficacies affect antiviral responses, specifically viral load and T-cell count.

In the long term of HIV treatment, the drug concentration varies during the dose intervals. Once a dose is administered, drug concentration gets high and reaches a peak value. As time passes by, the concentration gets lower. When another dose is administered, drug concentration repeats the same cycle. It is natural to assume that drug concentration varies periodically, which results in periodic variation of the drug efficacy. Yang and Xiao[21] formulated following simple model with periodic drug efficacy and investigated the interaction dynamics of T-cells and virus.

$$\begin{aligned} T'(t) &= \lambda - dT - k(1 - n_{rt}(t))VT, \\ T^{*'}(t) &= k(1 - n_{rt}(t))VT - \delta T^*, \\ V'(t) &= N\delta T^* - cV. \end{aligned} \tag{7}$$

Yang and Xiao got a threshold value of (7) between the extinction and the uniform persistence of the disease by applying the persistence theory. The disease goes to extinction if the threshold value is less than unity, while the disease persists if the threshold value is larger than unity. There exists a positive periodic solution which is globally asymptotically stable. Their conclusion extended the classic results for the basic autonomous model.

Based on Dixit and Perelson[19] model, we extend system (5) to include pharmacokinetics of drug therapies.

$$\begin{aligned} T'(t) &= \lambda - dT(t) - (1 - n_{rt}(t))kV_I(t)T(t), \\ T^{*'}(t) &= (1 - n_{rt}(t-\tau))kV_I(t-\tau)T(t-\tau)\mathrm{e}^{-m\tau} - \delta T^*(t), \\ V_I'(t) &= (1 - n_p(t))N\delta T^*(t) - cV_I(t), \\ V_{NI}'(t) &= n_p(t)N\delta T^*(t) - cV_{NI}(t). \end{aligned} \tag{8}$$

The time-varying parameters $n_{rt}(t)$ and $n_p(t)$ are the RTIs and PIs drug efficacies at time t, respectively. The challengeable problem of (8) is to determine the expressions of $n_{rt}(t)$ and $n_p(t)$ since there is no good way to get them by laboratory experiment. We are trying to collect parameter values and treatment data to investigate the dynamics of (8) by numerical simulations.

4.2 Mutation and drug resistance

HIV does not always make perfect copies of itself. With billions of virions being made every day, small and random differences can happen. The differences are called mutations. Mutations can keep the drugs from working, leading to the reduction in effectiveness. This is called drug resistance. The drug resistance is closely related to the mutation and poor adherence. Adherence means taking your medications on time, taking the prescribed dose, and taking them the correct way (with or without food, for example).

The emergence of drug resistance is one of the most prevalent reasons for treatment failure in HIV therapy. There are a lot of mathematical models concerning the population dynamics, HIV

treatment and drug resistance[5,22,23]. Recently, Rong *et al*[22] assumed that the drug-sensitive and resistant strains differ by a single mutation. They first showed that for chronically infected HIV patients the drug resistant strain exists before the initiation of antiretroviral therapy (ART). The model is the following system of differential equations

$$\begin{aligned} T'(t) &= \lambda - dT - k_s V_s T - k_r V_r T, \\ T_s'(t) &= (1-u)k_s V_s T - \delta T_s, \\ V_s'(t) &= N_s \delta T_s - cV_s, \\ T_r'(t) &= uk_s V_s T + k_r V_r T - \delta T_r, \\ V_r'(t) &= N_r \delta T_r - cV_r, \end{aligned} \tag{9}$$

where, $T_s(t)$ and $T_r(t)$ are the concentrations of T-cells productively infected by drug sensitive virus and drug-resistant virus, respectively; $V_r(t)$ and $V_s(t)$ represent the concentrations of drug sensitive and drug-resistant virus, respectively. k_s and k_r represent the rate constants at which uninfected cells are infected by drug sensitive and drug-resistant virus, respectively. $u\,(0 \leq u < 1)$ is the rate at which cells infected by the drug sensitive virus mutate and become drug-resistant during the process of reverse transcription of viral RNA into proviral DNA. Both types of infected cells are assumed to have the same death rate δ. They supposed that the drug sensitive and resistant strains differ in their burst sizes, N_s and N_r, while they have the same virion clearance rate c. It should be noted that the backward mutation from drug-resistant to drug-sensitive strain is neglected since the wild-type virus dominates the population before the initiation of therapy[7]. They assumed both the infection rate and burst size of resistant strain are less than those of wild-type strain, i.e., $k_r < k_s$ and $N_r < N_s$.

Those authors aimed to study the virus dynamics as well as the development of drug-resistant strains. They gave the basic reproductive numbers of the wild-type strain $\mathcal{R}_s$ and the drug-resistant strain $\mathcal{R}_r$, respectively, $\mathcal{R}_s = (k_s N_s \lambda)/(dc)$ and $\mathcal{R}_r = (k_r N_r \lambda)/(dc)$. They got following results:

1) The infection-free steady state E_0 is locally asymptotically stable if $\mathcal{R}_s < 1/(1-u)$ and $\mathcal{R}_r < 1$, and it is unstable if $\mathcal{R}_s > 1/(1-u)$ or $\mathcal{R}_r > 1$.

2) The steady state with only drug-resistant virus, E_r, exists if and only if $\mathcal{R}_r > 1$. It is locally asymptotically stable if $\mathcal{R}_r > (1-u)/\mathcal{R}_s$ and unstable if $\mathcal{R}_r < (1-u)/\mathcal{R}_s$.

3) The coexistence steady state E_c exists and is locally asymptotically stable if and only if $\mathcal{R}_s > 1/(1-u)$ and $\mathcal{R}_r < (1-u)/\mathcal{R}_s$.

With parameter values $\lambda = 10^4$ ml^{-1}day^{-1}, $d = 0.01$day^{-1}, $k_s = 2.4 \times 10^{-8}$ ml day^{-1}, $k_r = 2.0 \times 10^{-8}$ ml day^{-1}, $u = 3 \times 10^{-5}$, $\delta = 1$day^{-1}, $N_s = 3000$, $N_r = 2000$ and $c = 23$day^{-1}, Figure 3 shows simulation results for the T-cells count and viral loads of both the wild-type and drug-resistant strains before treatment. The wild-type virus dominates the virus population before the initiation of ART.

4.3 Impulsive drug effects

Recently, Smith and Wahl[24,25] described the drug concentrations during HIV therapy using impulsive differential equations, considering the dynamics of T-cells interacting with free virions, reverse transcriptase inhibiting drugs and protease inhibiting drugs. In [24], they divided T-

cells into six classes and found that insufficient dosing of either drug corresponds to high viral load and a large population of infectious T cells. They further predicted that, in the absence of physiological limits on tolerable drug concentrations, sufficiently frequent dosing with the RTI alone could theoretically maintain the T-cell count close to the uninfected case. However, for frequent dosing of the PI alone, the limiting T-cell populations may not be enough to maintain the immunity. Furthermore, frequent dosing of both drugs has the same effect on the T-cell population as frequent dosing of the single RTI. Those two drugs can have fundamentally different effects on the long-term dynamics and the RTI, in particular, plays a crucial role in maintaining the immunity. In [25], different regimes were classified according to whether the drug efficacy is negligible, intermediate or high. Two strains of virus were considered: a wild-type strain that can be controlled by both intermediate and high drug concentrations, and a mutant strain that can only be controlled by high drug concentrations. It was discussed if dosing schedules and concentrations of preventative drugs facilitate or prevent the emergence of drug resistance. The estimates of a range of dosages and dosing schedules which would, if physiologically tolerable, theoretically eliminate free virus in this system were provided. Their results predicted that decreasing the interval between doses was more effective than increasing the dose to control viral load.

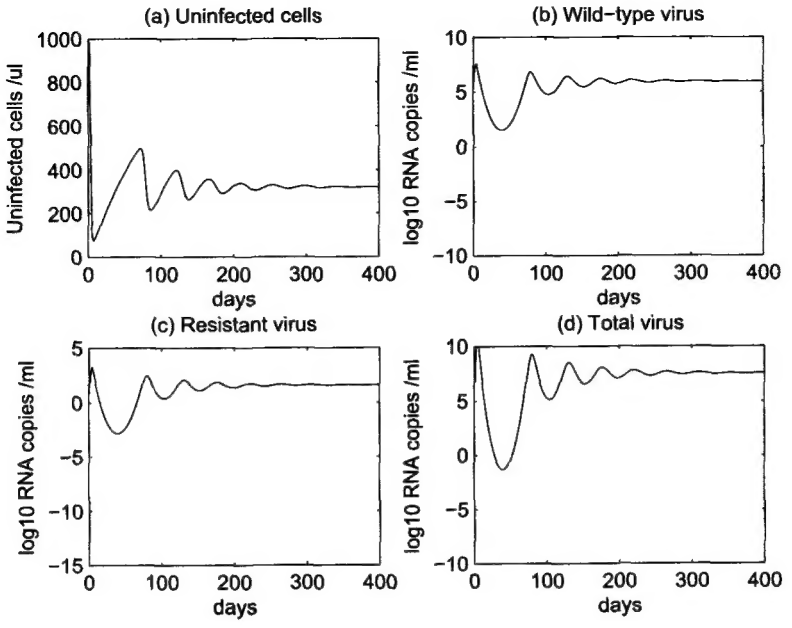

Figure 3: Simulation of uninfected T-cells and viral loads of both wild-type and drug-resistant strains for the pretreatment model (9). The basic reproductive numbers for two strains are $\mathcal{R}_s = 3.13$ and $\mathcal{R}_r = 1.74$. Before treatment, both strains of virus coexist. However, the drug-resistant strain remains at a very low level after an initial increase and the wild-type virus dominates the population

5 Conclusion and discussion

We have presented a number of dynamical models and results on the study of HIV dynamics. We have tried to demonstrate how mathematical modeling can help us to understand HIV pathogenesis. The interaction of T-cells and virus, time delay, drug therapy and drug resistance are discussed in different models. Mathematical modeling and computer simulations are powerful tool to improve the design of AIDS clinical trials, to study the pathogenesis of HIV infection, to estimate the parameter values, and to evaluate new treatment strategies[20].

Most of the mathematical models can be extended to a more general system

$$\dot{x} = f(x)(\text{or } f(x,y)) - xz, \quad \dot{y} = xz(\text{or } x(t-\tau)z(t-\tau)) - y, \quad \dot{z} = y - z,$$

which, for example, can be used describe the interaction of caterpillars x, parasitic wasps z and parasitized caterpillars y. Those models and results can be applied in other settings beyond the HIV dynamics. It is hopeful to obtain more mathematical results and richer dynamics for the model with a general function f.

Although there are plenty of mathematical models and simulations, there still a long way for us to understand the HIV pathogenesis completely. There are many interesting and challengeable topics in modeling and dynamics of HIV infection and treatment.

5.1 Age and infection age structures

Age and infection age are important factors in HIV infection and disease progression. Age-structured models have been widely used to study the epidemiology of infectious diseases. Nelson *et al*[26] developed an age-structured model of HIV infection and showed that the age-structured model is a generalization of ODE and DDE models. Age-structured models have greater flexibility that may help us to understand the underlying mechanism of HIV infection and treatment better[27]. Infection age-structured model may be more appropriate in describing the disease progression and treatment since HIV takes about 10 years, on average, to progress from initial infection to AIDS, T-cell count and viral load varying a lot in different stages of infection. Infection age-structured model may give better simulation and assessment result of a treatment strategy.

5.2 Intermittent treatment

Kirschner and Webb[23] showed that a possible strategy, intermittent treatment, may have advantage in reducing side effects or resistance. Intermittent strategy is to treat with chemotherapy followed by interruptions in the treatment during which either a different drug or no treatment is administered. Recently, the Strategies for Management of Antiretroviral Therapy (SMART) Study Group[28] found that the intermittent ART guided by the $CD4^+$ count significantly increased the risk of opportunistic disease or death from any cause, as compared with continuous ART, largely as a consequence of lowering the $CD4^+$ cell count and increasing the viral load. Intermittent ART does not reduce the risk of adverse events that have been associated with ART. However, because of the poor adherence in reality, or by other interruption of treatment, it is necessary to investigate the intermittent treatment.

5.3 HIV co-infection with other diseases

Kirschner[29] indicated that co-infection may indeed play a dramatic role in diseases. He found that the T-cell populations are lower in the presence of both M. tuberculosis and HIV

than in the case of infection with HIV alone. Also, the viral load and M. tuberculosis population are higher in the co-infected patient, than the single-pathogen infection cases.

Co-infection with hepatitis C virus (HCV) and HIV is common in certain populations. Among HCV(+) persons, 10% are also HIV(+), and among HIV(+) persons, 25% are also HCV(+). Many studies have shown that in intravenous drug users, co-infection prevalence can be as high as 90-95%. There is increasing evidence supporting the concept that people infected with HIV have a much more rapid course of their hepatitis C infection[30]. HIV can also co-infection with Hepatitis B virus (HBV)[31].

5.4 Latent infection

Although the HAART is extremely effective in reducing the viral load, which resulted in a substantial reduction of morbidity and mortality, an HIV infected individual has not got complete recovery by the prolonged HAART. HIV can have latent infection in resting memory T-cells, which forms a cellular reservoir. The nature of memory T-cells have them remain in the resting state in the presence of HAART for a long time. The viral may rebound when HAART is withdrawn since reservoir releases new virus. Rong and Perelson presented a review on viral persistence, the latent reservoir, and mathematical models developed to explore their relationships[32]. Interested readers can have more information from their paper. Banks *et al* formulated a model to describe the pathogenesis of HIV infection including certain important features, such as the reservoir of latently infected cells[33]. That more biological models may admit multiple stable off-treatment equilibria, and can exhibit the phenomenon of transient viremia. They showed that the model provides reasonable fits to the patient data and, moreover, that it exhibits good predictive capability. They demonstrated that parameter values obtained for most clinical patients do not admit multiple stable off-treatment equilibria.

5.5 Parameter estimate and model fitting with data

In the development of mathematical models for the progression of HIV infection and treatment, the model dynamics should be in agreement with the mechanism and key features of HIV infection. In application of those models to HIV treatment the parameter values should be determined, and the model prediction should match with data. Adams *et al* discussed mathematical and statistical ideas relevant to structured treatment interruptions, including parameter estimation[34]. A nonlinear model was used to fit clinical data for HIV patients undergoing treatment interruptions. After the parameter estimation by a statistically-based censored data combined with inverse problem techniques the comparison between the model simulation result and observation data was demonstrated by many figures[35].

Although mathematical models and theoretical results have done great help to understand HIV infection and treatment, the model assumption and parameter estimation method should be improved to make the model and the application more biological and realistic. If we use model with constant parameters to describe the long term dynamics of HIV infection and treatment, it is usually found that the T-cell count and the viral load will tend to equilibrium states. The phenomenon tending to equilibrium states of those models does not match the biological observation. The T-cell count (the viral load) of an HIV infected individual will be very low (very high) after becoming AIDS without treatment. We are working to develop a model with time dependent parameters to simulate the complete progression of an HIV infected

individual. We determine those time-dependent parameters by comparing the model simulation result with the well known curves of T-cell count and viral load. After those parameters are confirmed, we can use the model to give more biological prediction on the disease progression and treatment.

There are also other challenging topics in HIV infection and treatment. 1) HIV treatment in a specific country: in a specific country, the environment, HIV transmission, the regimes of treatment, and the combination of ART may be different from other countries; 2) Time dependent drug efficacy: it is more realistic assumption for the interaction between pharmacokinetics and pharmacodynamics. We may obtain the expression among the regime treatment, drug efficacy with plasma concentration by experimentation; 3) Global dynamics: We do not have effective method to obtain satisfactory results on global dynamics. For most of the models, including our model[4], the global stability is still an open question. New theory and method need to be established.

6 Appendix

We have searched many references to determine the range of parameter values. We list them in the appendix so that our readers can consult easily, see Table 1 and all the parameters cited from[4].

Table 1: List of parameters

Parameter	Definition	Range of Parameters
λ	T-cells source term	0–10 $\text{mm}^{-3}\text{day}^{-1}$
d	Death rate of healthy T-cells	0.007–0.1 day^{-1}
r	Growth rate of T-cells	0.03–3day^{-1}
k_I	Viral infectivity rate	0.00025–0.5 $\text{mm}^3\text{day}^{-1}$
k_A	Rate infected cells becomes active	$k_A/k_I \approx 1$
δ	Death rate of infected T-cells	0.2–0.5 day^{-1}
$T_{\max}$	Carrying capacity of T-cells	1500 mm^{-3}
N	Bursting term for viral production after lysis	10–2500
c	Clearance rate of virus	2.4–3 day^{-1}
τ	Virus replication time	0–2 days
n_{rt}	Reverse transcriptase inhibitor efficacy	(0,1)
n_p	Protease inhibitor efficacy	(0,1)

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艾滋病毒感染后疾病进展和治疗的数学模型及其动力学性态

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摘 要: 本文是对个体被艾滋病毒感染后的数学模型及动力学性态研究情况的简单综述。介绍了$CD4^+$ T细胞、病毒颗粒和药物治疗相互作用的艾滋病数学模型的研究结果, 主要是用常微分方程、时滞方程、积分微分方程和脉冲微分方程来描述艾滋病感染后疾病进展和治疗的模型理论研究和数值模拟结果。我们收集了这些模型中基本参数值的取值范围, 将其整理成一个表格放在附录中以便读者参考。

关键词: 艾滋病毒; T细胞; 耐药性; 药物治疗; 时滞; 渐近稳定性